Identification of two APOBEC3F splice variants displaying HIV-1 antiviral activity and contrasting sensitivity to Vif.

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Public Summary:

Scientific Abstract:
Approximately half of all human genes undergo alternative mRNA splicing. This process often yields homologous gene products exhibiting diverse functions. Alternative splicing of APOBEC3G (A3G) and APOBEC3F (A3F), the major host resistance factors targeted by the HIV-1 protein Vif, has not been explored. We investigated the effects of alternative splicing on A3G/A3F gene expression and antiviral activity. Three alternatively spliced A3G mRNAs and two alternatively spliced A3F mRNAs were detected in peripheral blood mononuclear cells in each of 10 uninfected, healthy donors. Expression of these splice variants was altered in different cell subsets and in response to cellular stimulation. Alternatively spliced A3G variants were insensitive to degradation by Vif but displayed no antiviral activity against HIV-1. Conversely, alternative splicing of A3F produced a 37-kDa variant lacking exon 2 (A3FDelta2) that was prominently expressed in macrophages and monocytes and was resistant to Vif-mediated degradation. Alternative splicing also produced a 24-kDa variant of A3F lacking exons 2-4 (A3FDelta2-4) that was highly sensitive to Vif. Both A3FDelta2 and A3FDelta2-4 displayed reduced cytidine deaminase activity and moderate antiviral activity. These alternatively spliced A3F gene products, particularly A3FDelta2, were incorporated into HIV virions, albeit at levels less than wild-type A3F. Thus, alternative splicing of A3F mRNA generates truncated antiviral proteins that differ sharply in their sensitivity to Vif.

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